

NOTES ON A CASE OF
PAROXYSMAL METHÆMOGLOBINURIA.

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NOTES ON A CASE OF PAROXYSMAL METHÆMOGLOBINURIA.

LAST winter Dr Muirhead kindly asked me to examine a case of paroxysmal hæmoglobinuria, which had been lately admitted into Ward 29. I have now the pleasure of laying some notes of the case before the Society.

George M'V., aged 26, married, a hawker, was admitted into the Edinburgh Royal Infirmary on November 25th, 1890, complaining that his urine became at times very dark coloured. With a precarious employment, a poor home, often too scanty a supply of food, his experiences of life had not been of the happiest; he, however, had not indulged overmuch in liquor, and had enjoyed reasonably good health up to two years before admission into hospital. About that time he noticed that he became more prone to take cold; that if he were chilled in any way he was seized with a rigor; his urine, however, was normal as yet. These attacks grew more and more severe, and were accompanied by the passage, for a few hours after an attack, of dark porter-coloured urine. His description of a severe attack was as follows:—On going out on a cold day he would suddenly become chilled all over, benumbed, with acute pain in the stomach region, so acute sometimes as to double him up; he would then eructate much wind, with great relief to himself. During the attack he felt giddy, but never fell, while his testicles were retracted and his skin muscles contracted, causing a condition of goose-skin. There never was any pain over the kidneys.

His first severe attack occurred when he was watching some races at Powderhall on a very cold day,—he was not sure of the date, probably in spring 1890,—while since then he has passed blood in the urine once or twice every week. He does not appear to have had syphilis, nor has he ever been abroad. There was no correspondence, as far as I could ascertain, between drink and the disease.

Condition on admission.—A very small, badly-developed man, miserably nourished, height 4 ft. 10 $\frac{3}{4}$ in., weight 6st. 9 lbs., obviously anæmic. Physical examination revealed no abnormality, his tongue was a little flabby and furred, his bowels slightly costive.

Analysis of the urine on admission gave the specific gravity as 1024, reaction acid, no albumen or sugar, urea 7·4 grs. per ounce, or the amount of urine being 36 ounces in the twenty-four hours, 266·4 grs. on a hospital diet. Temperature normal.

Progress.—The day after admission he was sent out for a walk; the weather happened, as usual, to be bad, and he came in with a temperature of 100° Fahr., reporting that he had not been long out before he began to shiver. On his return he passed some very dark urine. It was at this stage that I was asked to examine the case more carefully, and was given a sample of the dark urine passed the day before for analysis. As the urine passed during the attack had been mixed with the urine previously passed, I contented myself here with a determination of the pigment. On examining it with the spectroscope, I found the four bands which are characteristic of acid hæmatin, and which further were not reduced to the one broad band of reduced hæmoglobin on the addition of a small quantity of ammonium sulphide. There were no blood corpuscles or casts, and the fluid, which was faintly acid, deposited only a small quantity of dark granular debris.

For six days after this attack the patient was kept quietly in bed, and was given 3j. doses of the liquid extract of ergot every eight hours. On the sixth day I tested his urine and examined his blood. The urine was 1016, acidity ·1008 per cent. (reckoned as HCl), no albumen, sugar, or blood, urea 107·5 grs., no deposit; while the blood contained 3,100,000 red corpuscles, which were irregular and crenated, some having vacuoles in them. The white corpuscles, 100,000, were above the normal. The amount of hæmoglobin present was 65 per cent., that is, the proportion per corpuscle was $\frac{65}{2\frac{1}{2}}$, or 104·8 per cent. On the 4th of December, two days later, the examination of the blood showed that the number of red corpuscles had increased to 3,370,000; the hæmoglobin was 63 per cent., or 93·4 per cent. per corpuscle. The pigment present was oxyhæmoglobin, the red corpuscles were from 6 to 8 μ in breadth, no very small ones, but some tailed and others crenated. White corpuscles 20,000. Plates numerous.

The urine for the day before contained 8·4093 grs. of urea per oz., or 319·55 grs. per diem, had a specific gravity of 1021, a deposit of mucus and oxalates, and an acidity of ·18 per cent. HCl, or ·06624 gram. of HCl in the day.

The urine of the 4th contained 5·8325 grs. of urea per oz., or 225·3 grs. altogether, the specific gravity was 1020, acidity ·054 per cent., or ·0216 gram. of HCl per diem; there was a deposit of phosphates and mucus.

On the 5th he was allowed up and about the ward, and on the 6th the red corpuscles numbered 3,080,000, the white 10,000, the plates were not so numerous, while the red corpuscles, measuring from 6 to 10 μ , were larger, and were neither tailed nor crenated. The hæmoglobin was 63 per cent., or 103·2 per corpuscle. Urine:

sp. gr., 1020; acidity, .126 per cent., or .05796 gram. per diem; urea, 7.0726 grs. per oz., or 325.33 grs. Oxalates present; no albumen or blood.

7th December.—He was up all day yesterday. He had some slight diarrhœa, his bowels moving thrice. The urine was more concentrated; sp. gr., 1024; acidity, .216 per cent., or .07344 gram.; urea, 12.221 grs. per oz., or 415.514 grs. per diem.

8th December.—Up all yesterday, but not allowed out. Blood analysis shows the number of red corpuscles to be 3,990,000, the hæmoglobin 55 per cent.; proportion per corpuscle, 68 per cent.; white corpuscles 12,000; plates more numerous. The red corpuscles were from 7 to 10 μ in size, some were mere phantoms with only the outer envelope, and were discoloured, but of full size; one or two corpuscles were tailed, none crenated. Urine: sp. gr., 1020; acidity, .108 per cent., or .05832 gram.; urea 6.911 grs. per oz., or 373.194 grs. per diem. No albumen or blood.

9th December.—Urine: sp. gr. 1020; acidity, .144 per cent., or .06048 gram.; urea, 7.0972 grs. per oz., or 298.0824 grs. per diem. Patient had been out for a short time the day before, but did not feel cold; temperature, 54° Fahr.

10th December.—Yesterday he was sent out for most of the day somewhat thinly clad; on coming home he passed a few drops of dark-coloured urine, which were unfortunately mixed with the day's total. He neither felt the shivering nor the malaise which had formerly occurred. His temperature rose in the evening. Blood analysis: Red corpuscles, 2,200,000, from 4 to 7 μ in size; many more were irregular than in the last counting; none, however, tailed or crenated. No large ones seen, but many (about 60,000) small, colourless, ill-defined corpuscles, which were neither granular nor refracting. No pigment granules seen. Hæmoglobin, 70 per cent., or 159 per cent. per corpuscle. Spectrum gives only the oxyhæmoglobin bands. Urine, sp. gr. 1022, with a deposit of very small oxalate of lime crystals. Albumen and blood present. The pigment was very dilute, and gave the bands of oxyhæmoglobin, and more faintly those of methæmoglobin. These bands were reduced on the addition of ammonium sulphide. The total proteids were only .108 per cent., of which the serum albumen formed .025 per cent., the serum globulin .083 per cent. The urea, 7.0513 grs. per oz., came to 253.84 grs. in the day; the acidity, .108 per cent., or .03888 gram. The liver had been mapped out before, and showed no change; but the spleen was enlarged downwards and forwards, coming forward nearly as far as the nipple line at the level of the eighth or ninth ribs. There was no tenderness.

12th December.—He was out again for a short time yesterday, but had no attack. To-day the urine is clear; no blood or albumen; sp. gr., 1017; urea, 6.3054 grs. per oz., or 290.048 grs. per diem; acidity, .108 per cent. HCl, or .04968 gram. Blood analysis: Red

corpuscles, 3,530,000, size 6 to 9 μ ; some tailed, not so irregular as yesterday. White corpuscles, 15,000. Plates as usual. Hæmoglobin, 66 per cent., or per corpuscle 93·4 per cent. The spleen, if anything, is smaller than yesterday.

15th December.—Yesterday the day was colder, and although only out about three hours he felt very cold; he did not shiver, however. Temperature up; urine dark red. Blood analysis: Red corpuscles, 2,980,000, of various sizes, from 5 to 9 μ ; none tailed or vacuolated, but one or two very shadowy. White corpuscles, 20,000. Plates numerous. Hæmoglobin, 64 per cent., or 107·3 per cent. Urine the colour of port wine, clear, no deposit; sp. gr., 1031; no sugar; acidity, ·162 per cent., or ·08748 gram. per diem; urea, 9·524 grs. per oz., or 514·296 grs. altogether. The pigments present in the urine were oxyhæmoglobin and a trace of methæmoglobin, the lines distinctive of the latter only being visible in a thick layer of the fluid. The proteids present were ·6 per cent., of which serum albumen formed ·25 per cent., the globulin ·35 per cent. His spleen had again enlarged, but was not tender.

On the 16th the hæmoglobin had risen to 70 per cent., the red corpuscles to 3,850,000, or 90·9 per cent. per corpuscle. One or two phantom corpuscles, while the red cells as a rule were smaller but more regular, 4 to 6 μ in size, forming fairly good rouleaux. Urine: pale, deposit of mucus; sp. gr., 1025; urea, 232·96 grs. in the day; acid, ·03024 gram. No albumen or blood.

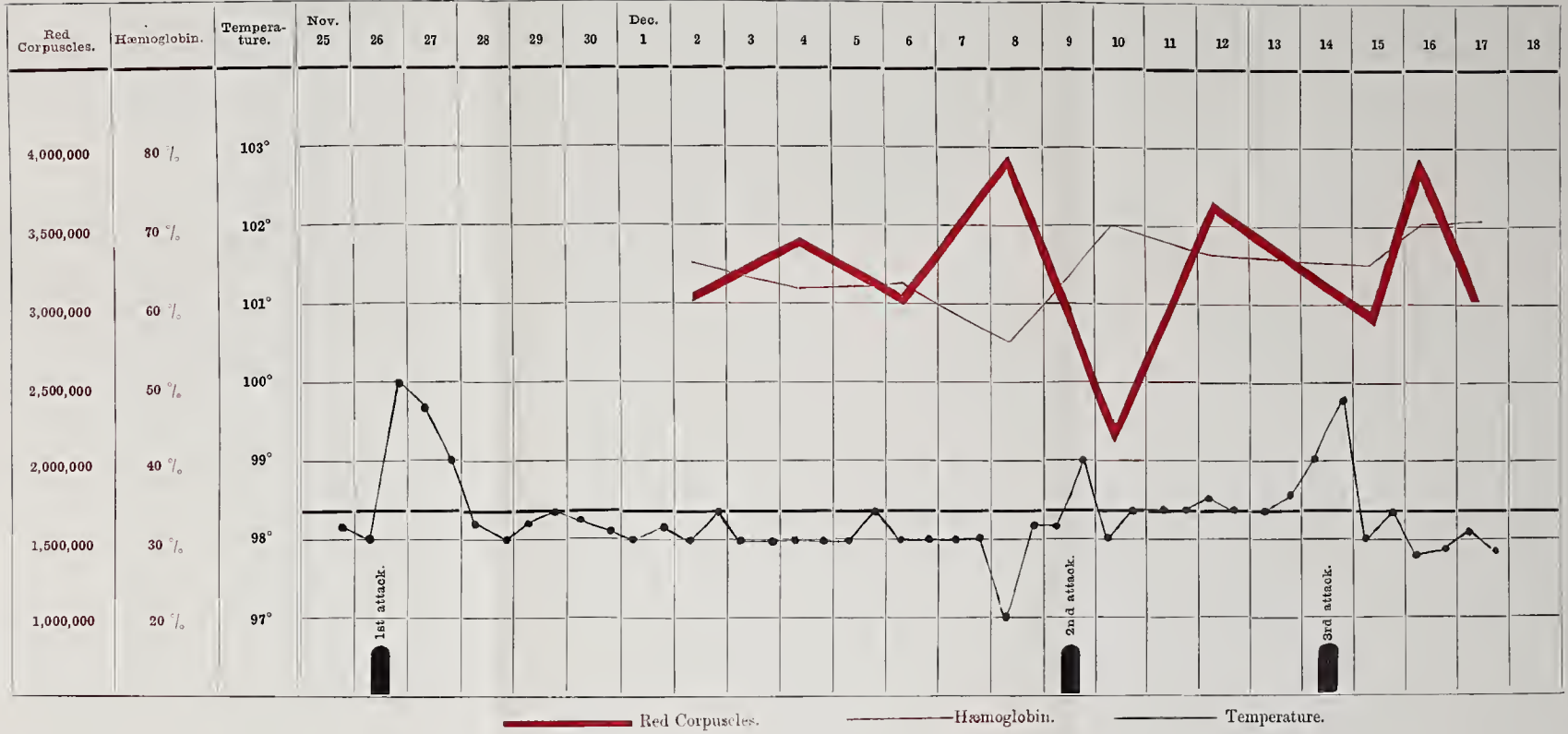
Seeing that his blood was in such an unstable condition, I resolved to try the effect of sulphonal on it, so I gave him 20 grs. on the night of the 16th. On the 17th his blood contained 2,930,000 red corpuscles, many of which were phantom; size, 5 to 8 μ ; none crenated, many elongated. Hæmoglobin, 70 per cent., or 119 per cent. per corpuscle. Urine contained no albumen or uro-hæmato-porphyrin, and was normal.

I gave him 30 grs. of sulphonal that night again, with no discoloration in the urine, and 35 grs. on the following night, with a similar want of success. He now expressed a desire to go home, so that I had to stop my observations. On dismissal he felt and looked very much better.

Conclusions.

The points I would particularly draw attention to are—first, the enlargement of the spleen with each attack; second, the fact that the percentage of hæmoglobin did not fall *pari passu* with the corpuscles; third, that the total urea excreted during the day increased on the day of the attack, contrary to what is otherwise affirmed (*Münchener Medicinischer Wochenschrift*, 1888, xxxv., pp. 495, 529, and 535). The proteids, too, merit attention, as does the temperature. The size of the corpuscles, also, varies after the attacks.

CHART I.

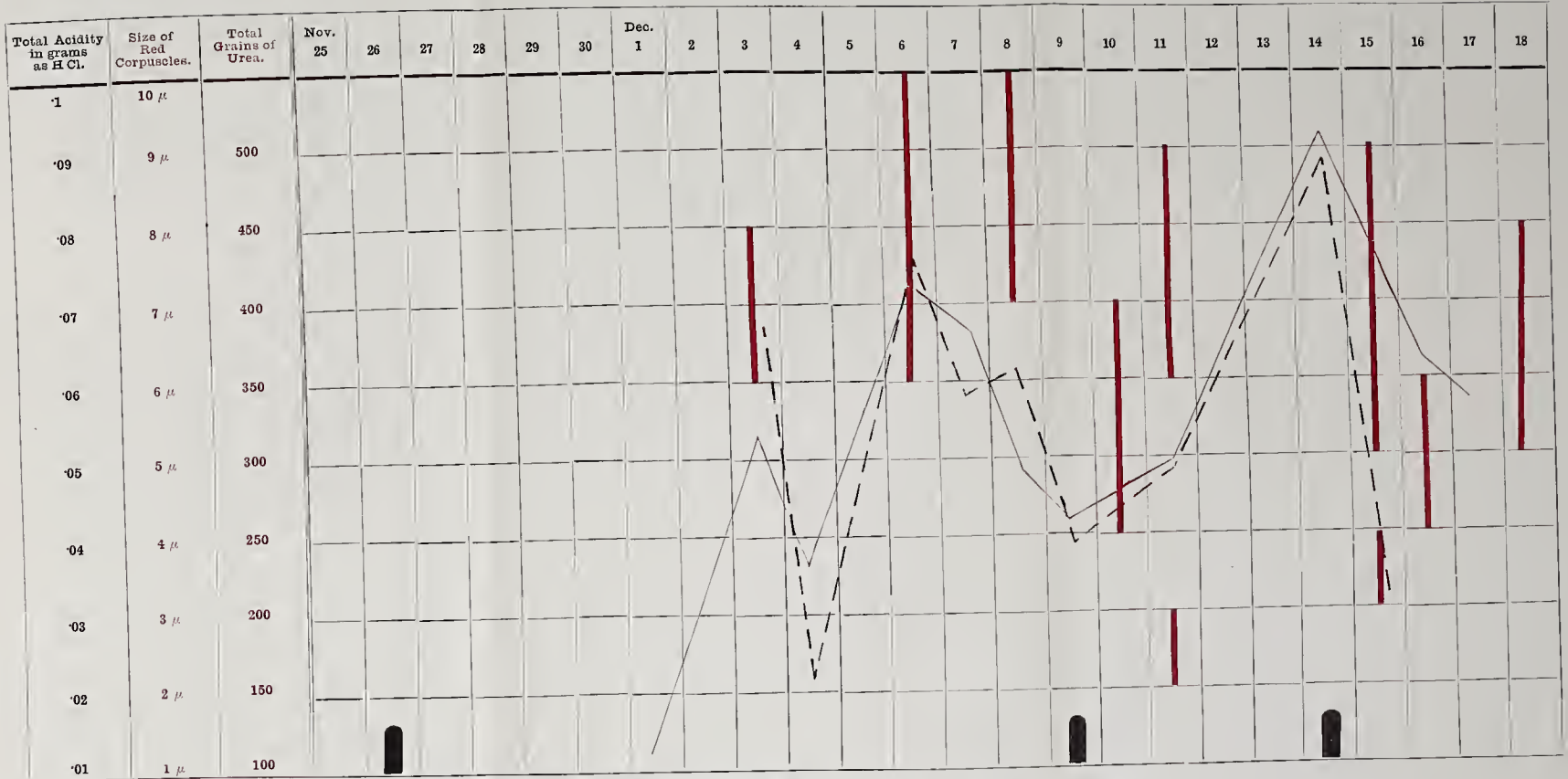




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CHART II.



The red line denotes total grains of urea per diem.
 The perpendicular red lines are intended to represent the variations in the size of the red corpuscles.
 The broken black line represents the total acidity of the urine in grams of H Cl.
 The thick black marks indicate the attacks.

The enlargement of the spleen, which occurred in this case, was coincident with the formation of numbers of young red blood-corpuscles.

Paroxysmal hæmoglobinuria is a local disease and yet a general one. The breaking down of the red corpuscles and consequent setting free of hæmoglobin occurs in the blood. This is shown conclusively by Boas' experiment, repeated by Copeman, of tying a ligature tightly round a finger, then dipping the finger into ice-cold water. Examination of the blood of this finger now shows free pigment in the plasma, with a loss of the power, inherent in the red cells, of forming rouleaux. There is little or no general disturbance. If both the hands, however, are placed in iced water for a short time, there is a decided disturbance, and pigment may or may not appear in the urine. Again, it has been pointed out that if a small quantity of hæmoglobin be injected into the blood of a healthy individual, none of it appears in the urine; if a little more be injected, some albumen may make its appearance; but on injecting large quantities, analysis of the urine shows the presence both of hæmoglobin and albumen. So in a case like this, if the disturbance be great and the tale of corpuscles destroyed large, the urine becomes porter-coloured. If the exciting cause be not so severe, only serum albumen and globulin may appear, constituting paroxysmal albuminuria. While on other occasions I believe you may get a slight attack with no striking evidences of it in the urine, a slight rise of temperature and diminution of red cells in the blood would be the only symptoms, along with a slight excess in the normal pigments of the urine. That is to say, then, that the organs of the body—principally, of course, the liver—can get rid of a certain quantity of free hæmoglobin; if the blood, however, be surcharged with it, it is eliminated by the kidney. Whenever sufficient has been excreted to allow the liver to deal with it in the ordinary way, the discharge in the urine ceases.

I will not enter into the subject of the elimination of proteids in the urine without coincident disease of the kidney tissue. It opens too wide a field. Selective affinity, and perhaps change and increase of blood-pressure, may partly account for it. In this case the serum globulin was in excess in the blood and in the urine. In ordinary cases of Bright's disease, the serum albumen is in excess. Excess of globulin over albumen in the urine is said to be due to increased blood-pressure.

Red blood-corpuscles are now formed in great numbers to make up for the deficiency caused by the previous destruction; and if the observation that the spleen enlarges after the attacks is confirmed, it is good evidence that the manufactory of the young cells may take place there.

The variation in the size of the red corpuscles is very instructive, apart from the mere irregularity and vacuolation of many of

the larger ones. On reference to Chart II., it will be seen that after the second attack the corpuscles varied from 4 to 7 μ on the day after, and on the next day from 2 to 3 μ and from 6 to 9 μ . After the third attack the sizes were from 2.5 to 9 μ . At the end of the considerable period that elapsed between the first and the second attack, the red corpuscles measured from 7 to 10 μ , or about the normal.

I tested the acidity of the urine each time, but with no result, save that as the urea increased so did the acid. Bearing in mind, however, the inverse proportion which always maintains between the acid eliminated by the kidneys and that present in the gastric juice, there is presumably a deficiency of acid in the stomach contents during and for some hours after an attack. This may account for the gastric symptoms detailed above.

With regard to the pigment present, on one occasion I found acid hæmatin, on three occasions methæmoglobin and oxyhæmoglobin, and in two other cases which I have seen, but which I had not an opportunity to examine further, the pigment was methæmoglobin. Copeman explains the presence of acid hæmatin by the action of the acid urine on the methæmoglobin, and asserts that the pigment, as originally secreted by the kidneys, is in the form of oxyhæmoglobin; this soon changes into methæmoglobin in the urine, and if left long enough, into acid hæmatin. Certainly after one of the attacks the urine I examined contained the latter pigment, as sulphide of ammonium had no effect on it, the four bands in the spectrum remaining as before. M'Munn, in 1889, asserted that methæmoglobin was the only pigment he had ever found in such cases. It is also certain, however, that the blood serum itself during an attack is stained not with methæmoglobin, but with oxyhæmoglobin.

The effect of nitrites and of chlorate of potash in inducing attacks has been tried in experiments with negative result.

About the time I was investigating the case, some attention was drawn to the appearance of uro-hæmato-porphyrin in the urine, following on the exhibition of sulphonal and allied hypnotics in large doses. Desirous of testing the effect of this drug on the evidently unstable corpuscles of this patient, I gave him, as recorded above, considerable doses of it each night, but with negative results. The patient, indeed, thought fit to end the treatment by abruptly leaving the hospital. The paper by Copeman in the *Practitioner* for 1890, p. 161, contains a fairly complete bibliography.

The analyses for the above were made at the Laboratory of the Royal College of Physicians, Edinburgh.